October 22, 1958

Dr. Mel Cohn
Department of Microbiology
Washington University
St. Louis, Mo.

Dear Mel:

I was really delighted to have a chance to have a good talk with you. Our interests have converged so much in the past it should not be surprising that they would make for a parallel approach on questions of antibody formation. This makes me all the more eager to get going at Stanford and see you at close hail.

You may be interested to see the enclosed project which I have thermofaxed from our application to NIH. I was only waiting to see you before writing up page 9, and trust this is sufficiently innocuous you can have no objection to having your workcited in that fashion. I think you will see why I was chuckling when you read the more fanciful projects.

On reflection, I am inclined to think that your immunization procedure may be the main reason for the discrepancy in our results. For example, by hyperimmunizing to one antigen, you were undoubtedly building up a large cellular population (pre-?)adapted to this; then by forcing a maximal response to a second antigen you may in effect be selected for a second-step 'mutation' in whatever cells were available. While this may be reasonably fatal to Burnet's'strong' version, it would not fit too badly with a weaker revision, which allows for further mutation to establish new specificities. To exclude the chromosomes as the actual sites of the 'mutations' it may be profitable to investigate whether a single cell can actually make a great many different antibodies: the cross-reaction studies may be the easiest approach to this. I don't know at what numerical point I would give up the chromosomes-- one might get tired of proving the point first, and among other things the diverse antibodies would have to be demonstrably related gamma globulins. But if it's not the chromosomes that are hypermutable, there are lots of microsomes, and I look forward to some difficulty in distinguishing between <u>election</u> among some millions of microsomes per cell versus instruction, at least until an in vitro system is worked out. In some ways, I think the very fact that cell fragments can make antibody is one of the most exciting prospects, and I hope we might be able to get Paul Berg interested in this in a more purposeful way. Has anybody seriously tried to demonstrate antibody synthesis *in vitro* in disrupted cell preparations? I assume one should use active, presensitized, secondary cells at the first trials.

Yours truly,

Joshua Lederberg